Cross-sectional area for the calculation of carotid artery stenosis on computed tomographic angiography

Anthony P. Carnicelli, BM, Jonathan J. Stone, MD, Adam Doyle, MD, Amit K. Chowdhry, BS, Doran Mix, BS, Jennifer Ellis, MD, David L. Gillespie, MD, and **Ankur Chandra, MD,** *Rochester, NY*

Objective: **The use of cross-sectional area (CSA) measurements obtained from computed tomographic angiography (CTA) for the calculation of carotid artery stenosis has been suggested but not yet validated in a large population. The objective of this study was to determine whether CTA-derived CSA measurements were able to predict carotid stenosis with a level of confidence similar to CTA-derived diameter measurements, using Strandness criteria applied to carotid duplex ultrasound (CDUS) as a surrogate for true stenosis.**

Methods: **A retrospective review was conducted to identify patients who underwent both CDUS and CTA between 2000 and 2009. Percent stenosis was calculated using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) formula with diameter measurements and again with CSA measurements. A nonparametric correlation coefficient was calculated to detect correlation between the two groups. Two-dimensional receiver-operating characteristic curves with corresponding area under the curve (AUC) statistics were generated for >50% stenosis and >80% stenosis. Three-dimensional receiver-operating characteristic plots with corresponding volume under the surface (VUS) statistics were generated to measure the comparative accuracy of diameter-based and CSA-based stenosis for <50%, 50%-79%, and >80% stenosis.**

Results: **A total of 575 vessels in 313 patients were included in the study. Spearman's correlation coefficient between diameter and CSA-derived stenosis was $\rho = 0.938$ (95% confidence interval [CI], 0.927-0.947; $P < .0001$). For diameter-derived stenosis, AUC was 0.905 (95% CI, 0.878-0.932; $P < .0001$) for >50% stenosis and 0.950 (95% CI, 0.928-0.972; $P < .0001$) for 80%-99% stenosis. For CSA-derived percent stenosis, the AUC was 0.908 (95% CI, 0.882-0.935; $P < .0001$) for >50% stenosis and 0.935 (95% CI, 0.908-0.961; $P < .0001$) for 80%-99%. The nonparametric estimate for VUS in the diameter-based stenosis group was 0.761, whereas in the CSA-based group, the VUS was 0.735. The difference between VUS was 0.026 (95% CI, −0.022 and 0.077; $P = .318$).**

Conclusions: **These data support the use of CTA as an accurate method of calculating carotid artery stenosis based on agreement with Strandness criteria applied to CDUS velocities. When additional imaging beyond CDUS is necessary, we report no significant difference between diameter and CSA measurements obtained from CTA for preoperative evaluation of carotid disease. (J Vasc Surg 2013;58:659-65.)**

Current recommendations suggest carotid duplex ultrasound (CDUS) to be the imaging modality of choice for screening the asymptomatic population at risk for carotid artery stenosis.[1] The Society for Vascular Surgery guidelines further suggest that additional imaging in the form of digital subtraction angiography (DSA), computed tomographic angiography (CTA), or magnetic resonance angiography be performed in patients with (1) nondiagnostic CDUS, (2) asymptomatic stenosis of intermediate severity, or (3) need for evaluation of vessels proximal or distal to the cervical carotid arteries.[1] With multiple imaging modalities available, disagreement has arisen among clinicians as to which technique offers the most accurate characterization of stenosis. The preferred imaging modality is often institution-specific and requires consideration of several variables including availability of angiography suites, use of nephrotoxic contrast, operator skill, and patient tolerance of the examination.[2-7]

Diameter measurements obtained from DSA have been the gold standard in the evaluation of carotid stenosis. This technique provided the clinical data needed to validate the use of velocity data obtained from duplex ultrasonography as a less invasive means of diagnosing carotid disease.[8-10] CTA, however, represents a less-invasive imaging option available for preoperative evaluation of patients in whom ultrasound results are nondiagnostic. CTA allows for multiplane diameter measurements, which may provide increased accuracy compared with measurements obtained from traditional two-dimensional DSA. Several studies support this conclusion, suggesting diameter measurements obtained from CTA may be as accurate as those obtained from DSA when used in the North American Symptomatic Carotid

From the Division of Vascular Surgery, University of Rochester School of Medicine and Dentistry.

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Reprint requests: Ankur Chandra, MD, Division of Vascular Surgery, University of Rochester School of Medicine and Dentistry, 601 Elmwood Ave, Box 652, Rochester, NY 14642 (e-mail: ankur_chandra@urmc.rochester.edu).

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Endarterectomy Trial (NASCET) equation for estimating carotid stenosis.[11-15] Furthermore, CTA may also provide useful prognostic information regarding plaque morphology such as ulceration and calcification.[16]

An additional benefit of CTA is the ability to obtain cross-sectional area (CSA) measurements of a stenotic vessel's flow lumen. One may hypothesize that CSA gives the best approximation of a vessel's flow lumen and, therefore, provides the most accurate depiction of carotid stenosis, particularly in the setting of an irregularly shaped lumen (Fig 1). Previous studies, however, report conflicting results as to whether an irregularly shaped lumen may introduce error into stenosis estimation using the NASCET equation.[17,18] The use of CSA measurements for the calculation of carotid artery stenosis has, therefore, been suggested but not yet validated in a large population. The objective of this study was to determine whether CTA-derived CSA measurements were able to predict carotid stenosis with a level of confidence similar to CTA-derived diameter measurements, using Strandness criteria applied to CDUS as a surrogate for true stenosis.

METHODS

A retrospective review was performed using a combination of International Classification of Diseases, Ninth Revision and Current Procedural Terminology codes to identify patients with suspected carotid disease who underwent both CDUS and CTA between 2000 and 2009 at the University of Rochester Medical Center. Data from both inpatient and outpatient imaging facilities were used in the study. Patients were included if they underwent CTA within 6 months of a CDUS study. Patients with complete occlusion of one carotid artery as demonstrated by computed tomography and confirmed by duplex were excluded from the study to prevent inclusion of patients with falsely elevated velocities.[19] Vessels with prior carotid endarterectomy or stent placement were excluded from the study. Patients with missing peak systolic velocity (PSV), end diastolic velocity (EDV), or PSV internal carotid artery/common carotid artery (ICA/CCA) ratio data on CDUS were also excluded from the study.

Variables collected included patient demographic information and CDUS velocities (PSV, EDV, and PSV ICA/CCA ratio). Diameter and CSA measurements at the point of maximum stenosis and at the distal ICA were obtained by a single study author after undergoing training and verification of measurement technique by an attending vascular surgeon. In heavily calcified vessels, an edge enhancement tool built into the imaging software was used to aid with delineation of the calcium-contrast interface. A sample ($n = 58$) of vessels was remeasured by both the author who obtained the original measurements and by a second study author to calculate intra/interobserver reliability. All study authors were blinded to patients' ultrasound velocities and clinical data prior to CTA measurement. All measurements were obtained from axial images. Distal measurements were taken at a disease free portion of the ICA no fewer than 2 mm distal to luminal stenosis. CSA measurements of the patent flow lumen were taken from the same axial slices that were used to obtain diameter measurements. CSA was quantified using Centricity RIS-IC software (v. 10.6.0.999; GE Healthcare, Little Chalfont, United Kingdom) with a built-in pixel-based image-processing algorithm requiring manual outline of the lumen being examined.

CTA studies were obtained using Philips Brilliance (Koninklijke Philips Electronics NV, Amsterdam, The Netherlands) 64-slice scanners imaging from the ascending aorta to the vertex in helical mode with 64- $\times$ 0.625-mm collimation, 100 kVp and 300 to 400 mA adjusted per patient size. Peripheral intravenous access was obtained with an 18- or 20-gauge catheter after confirmation of current lab values. A total of 75 mL of intravenous contrast was administered at a rate of 5 mL/s. A bolus-triggering technique was used with region of interest in the ascending aorta at the beginning of the aortic arch. Standard axial slices of 0.8 mm thickness at increments of 0.4 mm were obtained. Postprocessing reformats were subsequently performed but not used in this study.

Diameter measurements were used in the NASCET equation to determine diameter percent stenosis. Similarly, CSA measurements were used in the NASCET equation to determine CSA percent stenosis (Fig 2). Patients with stenosis calculations resulting in negative values were assumed to have 0% stenosis. Duplex velocities were used to quantify percent stenosis based on Strandness duplex velocity criteria for <50% stenosis (PSV $<$ 125 cm/s and EDV $<$ 140 cm/s), 50%-79% stenosis (PSV $>$ 125 cm/s and EDV $<$ 140 cm/s), and 80%-99% stenosis (PSV $>$ 125 cm/s and EDV $>$ 140 cm/s).

Three different methodologies were applied to assess differences between diameter and CSA-based techniques. First, a simple scatter plot comparing diameter percent stenosis vs CSA percent stenosis was generated, and Spearman's nonparametric correlation coefficient was calculated. Second, the ultrasound data were used as a surrogate for true stenosis for the creation of two-dimensional receiver-operating characteristic (ROC) curves. Strandness ultrasound criteria were used in two-dimensional ROC curve generation to divide the data in a binary (yes/no) fashion for >50% stenosis and again for 80%-99% stenosis. Area under the curve (AUC) was calculated for each ROC curve, and the difference between AUCs was tested statistically. Lastly, three-dimensional ROC surface plots were generated to describe the probability of correct classification into three diagnostic groups (<50%, 50%-79%, and 80%-99% stenosis) based on Strandness diagnostic thresholds. Volume under ROC surface (VUS) was calculated to measure the overall diagnostic accuracy of diameter-based and CSA-based stenosis. The difference between VUS values was calculated and statistically tested for differences. Conventional statistical analyses were performed using GraphPad Prism 6 (GraphPad Software Inc, La Jolla, Calif). The difference in AUCs for correlated ROC curves was tested using the pROC package in R software. DiagTest3Grp package in R software was

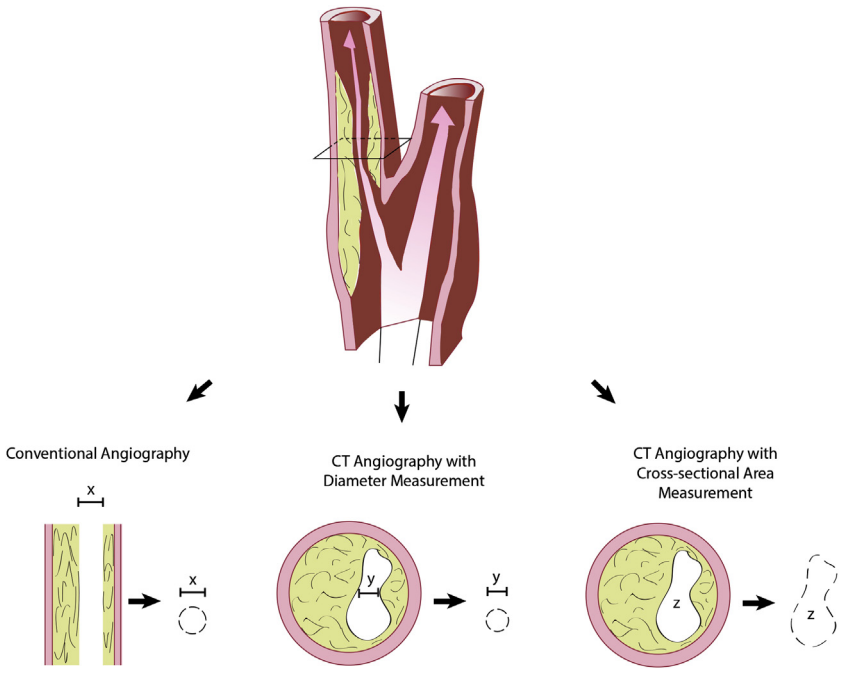

Fig 1. Graphic representation of the variability between commonly used measurement techniques for evaluation of carotid artery stenosis. *CT,* Computed tomographic.

$$\% \text{ Stenosis} = \frac{\text{Diameter}_{\text{poststenotic carotid}} - \text{Diameter}_{\text{maximum stenosis}}}{\text{Diameter}_{\text{poststenotic carotid}}}$$

$$\% \text{ Stenosis} = \frac{\text{CSA}_{\text{poststenotic carotid}} - \text{CSA}_{\text{maximum stenosis}}}{\text{CSA}_{\text{poststenotic carotid}}}$$

Fig 2. Top, Traditional North American Symptomatic Carotid Endarterectomy Trial (NASCET) method using diameter measurements to approximate carotid stenosis. **Bottom,** Investigational technique using cross-sectional area (*CSA*) measurements to approximate carotid stenosis.

used to calculate nonparametric estimates of VUS; 1000 Bootstrap resamples were performed to test for the difference in VUS.

RESULTS

A total of 575 vessels in 313 patients (136 females and 177 males) were included in the study (Table); 255 vessels were from females and 320 were from males. Mean age at ultrasound was 70.8 years (IQR, 63.5 − 80.7 years; SEM, 0.53 years). There were 43 vessels in the 80%-99% stenosis group, 201 vessels in the 50%-79% stenosis group, and 331 vessels in the <50% stenosis group. A comparison of diameter measurements with ultrasound data grouped by Strandness criteria for >50% stenosis yielded a sensitivity of 72.1%, specificity of 94.3%, positive predictive value (PPV) of 90.3%, and negative predictive value (NPV) of 82.1%. Similarly, CSA measurements for calculation of >50% stenosis yielded a sensitivity of 75.0%, a specificity of 93.1%, a PPV of 88.8%, and an NPV of 83.5%. Diameter measurements for calculation of 80%-99% stenosis yielded a sensitivity of 62.7%, a specificity of 97.2%, a PPV of 64.3%, and an NPV of 97.0%. CSA measurements for calculation of 80%-99% stenosis yielded

Table. Demographics, comorbidities, and medications

	Patients (n = 313)	*Vessels (n = 575)*	*Significance*
Mean age ± SD	70.7 ± 12.5	70.8 ± 12.7	$P = .91$
Male, No. (%)	178 (56.9)	321 (55.8)	$P = .77$
Female, No. (%)	135 (43.1)	254 (44.2)	$P = .77$
Comorbidities, No. (%)			
Diabetes	94 (30.0)	173 (30.1)	$P = .99$
Prior CVA	40 (12.8)	78 (13.6)	$P = .84$
Prior MI	33 (10.5)	60 (10.4)	$P = .99$
Documented CAD	104 (33.2)	188 (32.7)	$P = .88$
Smoking	166 (53.0)	300 (52.2)	$P = .83$
HTN	230 (73.5)	421 (73.2)	$P = .99$
Hypercholesterolemia	172 (55.0)	314 (54.6)	$P = .94$
Medications, No. (%)			
Beta blocker	144 (46.0)	266 (46.3)	$P = .94$
Aspirin	203 (64.9)	366 (63.7)	$P = .77$
Clopidogrel	53 (16.9)	93 (16.2)	$P = .78$
Warfarin	24 (7.7)	45 (7.8)	$P = .99$
Diuretic	102 (32.6)	180 (31.3)	$P = .71$
Calcium channel blocker	60 (19.2)	107 (18.6)	$P = .86$

CAD, Coronary artery disease; *CVA,* cerebrovascular accident; *HTN,* hypertension; *MI,* myocardial infarction; *SD,* standard deviation.
The column labeled Patients includes individual patients without duplicates, regardless of whether they contributed one or two vessels to the study. The column labeled Vessels allows for duplicates, as patients are counted twice if they contributed two vessels to the study.

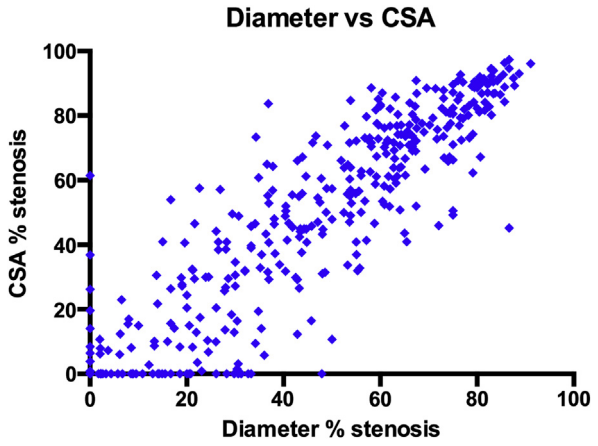

Fig 3. Scatter plot demonstrating correlation between stenosis calculated from diameter measurements vs cross-sectional area (*CSA*) measurements.

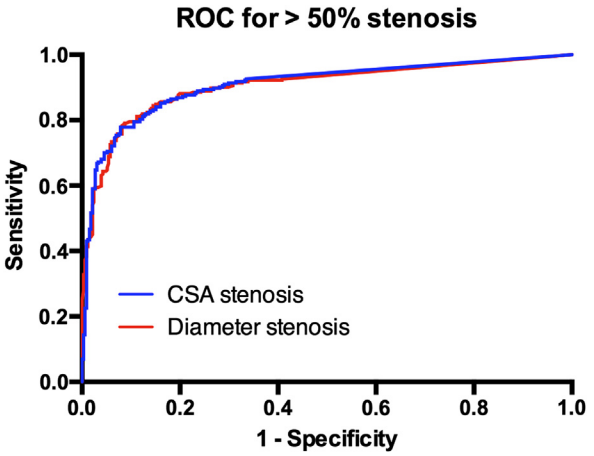

Fig 4. Receiver-operating characteristic (*ROC*) curves demonstrating the ability of both diameter measurements (*Diameter stenosis*) and cross-sectional area measurements (*CSA stenosis*) to detect stenosis of >50%.

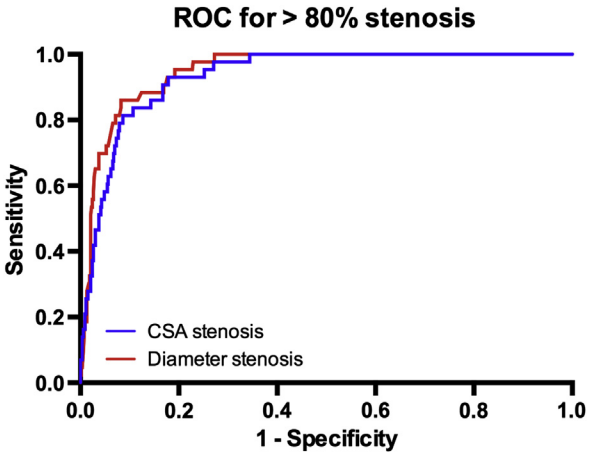

Fig 5. Receiver-operating characteristic (*ROC*) curves demonstrating the ability of both diameter measurements (*Diameter stenosis*) and cross-sectional area measurements (*CSA stenosis*) to detect stenosis of >80%.

a sensitivity of 79.1%, a specificity of 91.4%, a PPV of 42.5%, and an NPV of 98.2%. Spearman's correlation coefficient for intraobserver reliability was calculated to be $\rho = 0.951$ (95% confidence interval [CI], 0.919-0.971; $P < .0001$) for diameter measurements and $\rho = 0.957$ (95% CI, 0.929-0.975; $P < .0001$) for CSA measurements. Spearman's correlation coefficient for interobserver reliability was calculated to be $\rho = 0.838$ (95% CI, 0.740-0.901; $P < .0001$) for diameter measurements and $\rho = 0.901$ (95% CI, 0.837-0.940; $P < .0001$) for CSA measurements. A sample size of $n = 30$ vessels was calculated to yield 95% power to detect a correlation of 0.6 or greater. The sample size was subsequently increased to $n = 58$ to ensure sufficient power to detect a lower degree of correlation.

Spearman's correlation coefficient between diameter percent stenosis and CSA percent stenosis was $\rho = 0.938$ (95% CI, 0.927-0.947; $P < .0001$) (Fig 3). For diameter percent stenosis, AUC was 0.905 (95% CI, 0.878-0.932; $P < .0001$) for >50% stenosis (Fig 4) and 0.950 (95% CI, 0.928-0.972; $P < .0001$) for 80%-99% stenosis (Fig 5). For CSA percent stenosis, the AUC was 0.908 (95% CI, 0.882-0.935; $P < .0001$) for >50% stenosis (Fig 4) and 0.935 (95% CI, 0.908-0.961; $P < .0001$) for 80%-99% (Fig 5). The difference between AUCs for diameter and CSA for >50% stenosis was nonsignificant ($P = .675$) under alpha = .05. The difference between AUCs for diameter and CSA for 80%-99% stenosis was also nonsignificant ($P = .162$) under alpha = .05. The nonparametric estimate for VUS in the diameter percent stenosis group was 0.761 (Fig 6, *A*), whereas in the CSA percent stenosis group, the VUS was 0.735 (Fig 6, *B*). The difference between VUS was 0.026 (95% CI, −0.022 and 0.077; $P = .318$) showing nonsignificance under alpha = .05.

DISCUSSION

The use of CTA for the diagnosis and assessment of carotid stenosis is now a commonly used clinical tool when imaging beyond CDUS is required. Advantages of using CTA over DSA include its less invasive nature, the ability to obtain multiplanar views, and better visualization of plaque characteristics and morphology. Axial imaging and centerline reconstructive techniques allow radiographers to take precise three-dimensional measurements that were previously unobtainable with DSA. Both diameter and CSA of a vessel's flow lumen can be easily measured at various locations along the length of a stenotic vessel. Drawbacks to CTA include its inability to demonstrate important hemodynamic variables, nephrotoxic effects of contrast, exposure to radiation, and expense. Vessel tortuosity also poses a challenge when evaluating stenosis on axial images, although centerline

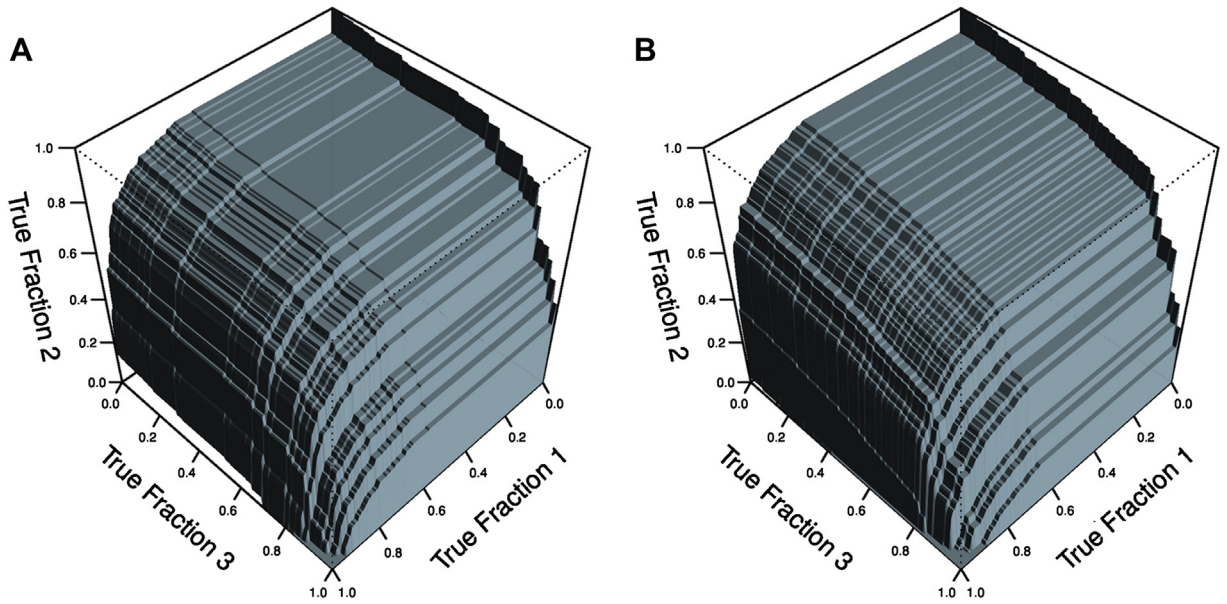

Fig 6. Three-dimensional receiver-operating characteristic (ROC) surface plots depicting the ability of diameter measurements **(A)** and cross-sectional area (CSA) measurements **(B)** to characterize carotid stenosis. *True fraction 1* describes the probability of the test correctly placing a patient in the <50% stenosis group; *true fraction 2* likewise for the 50%-79% stenosis group; and *true fraction 3* for the >80% stenosis group.

reconstruction may be employed in these instances to minimize ambiguities.

The use of CSA for evaluation of carotid stenosis is not a novel concept. Over a decade ago, Cinat et al described a high degree of correlation between true percent lumen reduction using CSA and both NASCET and European Carotid Surgery Trial (ECST) stenosis calculated from conventional angiographic measurements.[14] More recently, Prehn et al used diameter, CSA, and volumetric measurements to calculate both NASCET and ECST stenosis in a small cohort of patients.[20] The results demonstrate only modest correlation between CSA and duplex peak systolic velocities as well as a similarly modest correlation between CSA and duplex-based stenosis grading using Strandness grading criteria.[20] These results raise the question of whether such findings can be generalized to the more diverse target population of those patients in whom there is clinical suspicion of carotid disease.

Our study employs a large sample size to suggest that CSA percent stenosis can classify carotid disease as accurately as traditional diameter percent stenosis derived from CTA. This conclusion is supported by a lack of significant difference between ROC AUC values for >50% and 80%-99% stenosis categories. Spearman's correlation coefficient for diameter percent stenosis vs CSA percent stenosis also supports this conclusion. In addition, we suggest that ROC surface analysis using the VUS calculation is the most accurate and appropriate statistical measure of accuracy in this setting. The use of two-dimensional ROC curves limits investigators to the study of tests with binary outcomes, such as >50% or >80% stenosis. Two-dimensional ROC curves, therefore, provide no information about the important 50%-79% stenosis group. This third diagnostic group is sufficiently accounted for by ROC surface analysis, which is specifically designed to detect the overall accuracy of a diagnostic test in which there are three possible categorical outcomes. The three-dimensional ROC surface with VUS analysis has been shown to be both valid and reproducible in this setting.[21-25]

While some think of VUS as a three-dimensional version of the standard two-dimensional AUC, there are several key differences that make VUS a more appropriate test in our study. First, VUS calculations from ROC surface plots are designed to demonstrate the probability of accurately placing a patient with a given degree of stenosis into one of three categorical disease groups. Second, a VUS value of 0.167 may be thought of as similar to an AUC value of 0.5. In other words, both of these values describe a noninformative test. This can be conceptualized by understanding that VUS describes the probability that vessels from the <50% stenosis group, the 50%-79% stenosis group, and the 80%-99% stenosis group are correctly ordered. Since there are three factorial ($3! = 6$) ways to order the three groups, the probability of correctly ordering the three groups if the diagnostic test provides no information is $1/6 = 0.167$. In both the two-dimensional AUC and the three-dimensional VUS, a perfect test is defined by a value of 1. Our VUS data demonstrate a similar degree of accuracy between percent stenosis calculated from diameter vs CSA measurements.

One drawback of our study is the inability to test CSA and diameter measurements from CTA directly against DSA. The lack of a true gold standard in the study allows

for the possibility that all three of our diagnostic modalities (CDUS, diameter-based CTA measurements, and CSA-based CTA measurements) are equally inaccurate compared with DSA. Although we acknowledge this as a possibility, we suggest that this is not the case. We believe that Strandness CDUS criteria may, in certain circumstances, be used as a surrogate for the true gold standard, as these and similar criteria have been rigorously studied against DSA.[26-28] At our institution, it is not standard of care for patients to undergo DSA in the preoperative evaluation of carotid stenosis, and therefore, the vast majority of patients in our sample did not have DSA. Those patients with intraoperative DSA images saved in the imaging system unfortunately did not contain an object of reference within the images by which measurements could be calibrated. The direct comparison of DSA vs CSA measurements would be a meaningful study, although it would likely need to be performed in prospective fashion and would only include high-risk patients with unclear anatomy or those undergoing stenting.

Another potential limitation to this study is the assumption that carotid vessels within an individual patient can be treated as if they are independent of each other. There may in fact be a relationship between the severities of disease found within a single patient's carotid vessels, although this theory is not necessarily apparent within our dataset.

Last, although we are reporting a lack of significant difference between diameter and CSA measurements obtained from CTA, our study does not, however, address the question of whether CSA measurements are able to predict risk of stroke more or less accurately than diameter measurements. Additional trials are needed to evaluate whether CSA measurements provide additional information about clinical outcomes.

CONCLUSIONS

In conclusion, our data support the use of CTA as an accurate method of calculating carotid artery stenosis based on agreement with Strandness criteria applied to CDUS velocities. When additional imaging above CDUS is necessary, we report no significant difference between diameter and CSA measurements obtained from CTA for preoperative evaluation of carotid disease.

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AUTHOR CONTRIBUTIONS

Conception and design: APC, JS, AD, DM, JE, AC
Analysis and interpretation: APC, JS, AD, DM, JE, AC
Data collection: APC
Writing the article: APC
Critical revision of the article: JS, AD, AKC, DM, JE, DG, AC
Final approval of the article: DG, AC
Statistical analysis: APC, AKC
Obtained funding: APC, DG, AC
Overall responsibility: AC

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